IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#19
EBW
7-7-87

Applicant: Kohl et al

Serial No.: FWC of SN 748,591

Filed: herewith

For: DIALKOXYPYRIDINES, PROCESSES FOR THEIR PREPARATION, THEIR USE AND MEDICAMENTS CONTAINING THEM

Group Art Unit: 121

Examiner: Jane T. Fan

Honorable Commissioner of Patents
and Trademarks
Washington, D. C. 20231

April 24, 1987

Sir:

DECLARATION UNDER RULE 132

I, Uwe Krüger, being duly warned, declare and say:

1. THAT, I am a citizen of the Federal Republic of Germany, residing at Neuhauserstrasse 11, D-7750 Konstanz, Federal Republic of Germany.

THAT, from April 1959 to September 1964, I studied Chemistry (physical Chemistry with Mathematics and Nuclear-Chemistry as subsidiary subjects) at the Technical University of Braunschweig and, from August 1963 to September 1964, I did the practical work (electron diffraction at molecular gases) required for the degree of 'Diplom-Chemiker' (corresponding to the master degree) at the Physikalisch Technische Bundesanstalt in Braunschweig-Völkenrode. From September 1964 to November 1966, as a scientific assistant in the department of molecular spectroscopy at the Organic Chemical Institute of the Technical Universi-

ty of Braunschweig, I worked out my Thesis (initial Lewis acid complexes in Friedel-Craft reactions) and received the degree of Doctor (Dr. rer. nat.) at the end of this period. Post doctoral research (Nuclear Magnetic Resonance) followed with the Gesellschaft für Biotechnologische Forschung at Stöckheim until December 1969. From February 1970 to December 1973, I worked as a member of the scientific staff of the Philips Research Lab. in Hamburg in the field of Kerr liquids and Photochemistry.

THAT, in January 1974 I joined Byk Gulden Lomberg Chemische Fabrik GmbH, Constance, a pharmaceutical company, and, at present, I hold the position of the Head of the Department of Physical Organic Chemistry.

THAT, I have a 23 years experience in Physical Chemistry and good knowledge of Organic Chemistry.

THAT, I am the author and coauthor of numerous scientific publications including those on the attachment hereto.

2. THAT, with regard to structural and stability problems, I am fully conversant with the class of compounds of substituted 2-(2-pyridylmethylsulfinyl)-benzimidazoles as described and claimed, for example, in U.S. patent application FWC of SN 748,591 and U.S. patents no. 4,255,431, 4,435,406, 4,555,518 and 4,560,693.

THAT, the degradation of substituted 2-(2-pyridylmethylsulfinyl)-benzimidazoles is a known problem. Such degradation can be observed, for example, on storage as a solid (cf. U.S. patent 4,544,750, column 1, line 55), or in solution, in particular in an acidic environment (cf. U.S. patent 4,472,409, column 2, line 40), which leads to proton induced activation of the substance and rearrangement to its active principle [1, 2].

THAT, one of the main objects of the invention described and claimed in U.S. patent application FWC of SN 748,591 (cf. page 2, line 18) is to provide new 2-(2-pyridylmethylsulfinyl)-benzimidazoles (compounds of formula I of FWC of SN 748,591 with n = 1) which have, as compared with the 2-(2-pyridylmethylsulfinyl)-benzimidazoles known from the prior art, a higher chemical stability under those conditions, where a proton induced activation and rearrangement of the substance is not desired (i.e. under neutral conditions down to a pH of 5), such higher chemical stability being expected to correlate with the occurrence of less side effects.

3. THAT, comparative tests, which were made in order to compare the stability of the compounds of FWC of SN 748,591 with the stability of the compounds of U.S. patents no. 4,255,431, 4,435,406, 4,555,518 and 4,560,693, and which are described below in more detail, were performed in the laboratories of Byk Gulden Lomberg Chemische Fabrik GmbH, Konstanz, under my supervision and direction.

Comparative Tests

Compounds

The following compounds of U.S. patent application FWC of SN 748,591 (A) and U.S. patents no. 4,255,431 (B), 4,435,406 (C), 4,555,518 (D) and 4,560,693 (E) listed in Table 1 have been investigated in the comparative tests:

Table 1

Compound No.	Origin	Name
1	B	5-Methoxy-2-[(4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole
2	B	5-Methoxy-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole
3	B	5-Methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole
4	D	5-Difluoromethoxy-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole
5	A	5-Difluoromethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole
6	A	5-Difluoromethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole
7	D	2-[(4-Methoxy-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy--1H-benzimidazole
8	D	2-[(4-Methoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole
9	A	2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluoromethoxy-1H-benzimidazole
10	B	5-Ethoxy-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole
11	D	2-[(4-Methoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole
12	D	2-[(4-Methoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole

Table 1 (continuation)

Compound No.	Origin	Name
13	D	2-[(4-Methoxy-5-methyl-2-pyridyl)methylsulfinyl]-5-(1,1,2,2--tetrafluoroethoxy)-1H-benzimidazole
14	A	2-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole
15	A	2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole
16	A	2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5--(1,1,2,2-tetrafluoroethoxy)-1H-benzimidazole
17	D	2-[(4-Methoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole
18	A	2-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluoroethoxy)-1H-benzimidazole
19	B	5,6-Dimethoxy-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole
20	D	5-Difluoromethoxy-6-methoxy-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazole
21	A	5-Difluoromethoxy-6-methoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole
22	C	6-[(4-Methoxy-3-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]--dioxolo[4,5-f]benzimidazole
23	A	6-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole
24	E	2,2-Difluoro-6-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole
25	A	2,2-Difluoro-6-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole
26	A	2,2-Difluoro-6-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazole
27	C	6,7-Dihydro-2-[(4-methoxy-2-pyridyl)methylsulfinyl]-1H--[1,4]-dioxino[2,3-f]benzimidazole
28	E	6,6,7-Trifluoro-6,7-dihydro-2-[(4-methoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole
29	E	6,6,7-Trifluoro-6,7-dihydro-2-[(4-methoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole
30	A	6,6,7-Trifluoro-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazole

Objective

The gastric hydrochloric acid is produced in the parietal cells which are located in mucosal glands in the body and fundus of the stomach. The enzyme which regulates the production of hydrochloric acid in the parietal cells is the (H^+-K^+)-ATPase which therefore can be regarded as the proton pump in the secretory membrane of parietal cells. The inhibitory action of substituted 2-(2-pyridylmethyl-sulfinyl)-benzimidazoles on gastric acid secretion has to be attributed to inhibition of the (H^+-K^+)-ATPase.

Previous studies [1, 2] on the mode of action of this class of compounds have shown that their (H^+-K^+)-ATPase inhibiting activity is based on an acid induced transformation generating a highly thiophilic intermediate, which inhibits the (H^+-K^+)-ATPase by reaction with an essential SH-group of this enzyme. This acid activated transformation preferably should take place at a pH of 1-2, the pH of the acidic compartment of the parietal cell.

Since any reactions of the thiophilic intermediate with enzymatic SH-groups outside of the parietal cell could cause unwanted and unspecific side effects, acid activation should not or only to a small amount take place at those pH values which can be found **outside** the parietal cells.

Therefore, reactivity of the compounds should be as low as possible not only at the neutral pH (e.g. in the blood) but also at a pH down to the range of 5, which is reported for the lysosomes [3, 4], the cytoplasmic organelles in the body which enclose an acidic environment containing numerous enzymes capable of hydrolyzing most biological macromolecules. It was the objective of the invention described and claimed in U.S. patent application FWC of SN 748,591 to improve the specificity by reducing the reactivity at neutral pH down to a limit of pH 5. The stability in solution at pH 5 was used as the appropriate criterion for the selection of optimised structures which are still sufficiently reactive at pH < 2 and highly active in (H^+-K^+)-ATPase inhibition.

Method

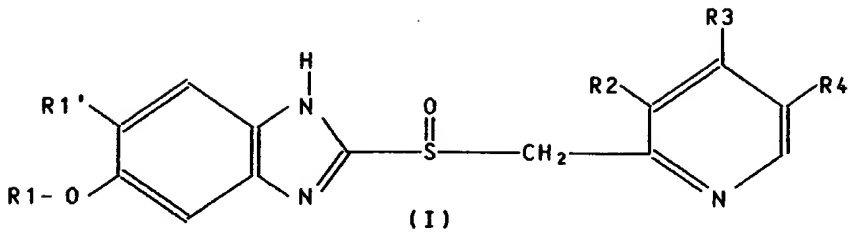
For determining the chemical stability as a measure for reactivity, the compounds to be investigated are dissolved in a 1:3 mixture of CH_3CN/H_2O (with addition of 0.01 M KH_2PO_4). The pH is adjusted to 5 with phosphoric acid. The addition of CH_3CN is needed for solubility reasons. The (pseudo first order) de-

cay of the compounds is monitored by repeated HPLC (High Pressure Liquid Chromatography) analysis over a period of time (e.g. 20, 45 and 55 hours for compounds 23, 26 and 25, respectively, otherwise around one half-life) sufficient to obtain concentration/time data for the calculation of half-lives by linear regression (ln concentration versus time).

Results

The stability data which resulted when the compounds of Table 1 were investigated according to the method described above in detail, are listed in the following Table 2. In order to facilitate the interpretation, the substituents of the investigated compounds were included in the table. Prior art compounds were marked with an asterisk. The value given in the last column is the half-life in hours, i.e. the time in which half of the compound decomposes in solution at a pH of 5.

Table 2



(I)

Compound No.	R1-O	R1'	R2	R3	R4	t 1/2(h)
1*	CH_3-O	H	H	CH_3O	H	6.0
2*	CH_3-O	H	CH_3	CH_3O	H	2.0
3*	CH_3-O	H	CH_3	CH_3O	CH_3	5.0
4*	CHF_2-O	H	CH_3	CH_3O	H	0.8
5	CHF_2-O	H	CH_3O	CH_3O	H	21
6	CHF_2-O	H	CH_3	CH_3O	CH_3O	23
7*	CF_3-O	H	H	CH_3O	H	4.0
8*	CF_3-O	H	CH_3	CH_3O	H	1.4
9	CF_3-O	H	CH_3	CH_3O	CH_3O	27
10*	CH_3CH_2-O	H	CH_3	CH_3O	H	1.3
11*	CHF_2CF_2-O	H	H	CH_3O	H	4.5
12*	CHF_2CF_2-O	H	CH_3	CH_3O	H	2.1
13*	CHF_2CF_2-O	H	H	CH_3O	CH_3	1.0
14	CHF_2CF_2-O	H	CH_3O	CH_3O	H	21
15	CHF_2CF_2-O	H	H	CH_3O	CH_3O	29
16	CHF_2CF_2-O	H	CH_3	CH_3O	CH_3O	26
17*	CF_3CH_2-O	H	CH_3	CH_3O	H	1.4
18	CF_3CH_2-O	H	CH_3O	CH_3O	H	10
19*	CH_3-O	CH_3O	CH_3	CH_3O	H	4.0
20*	CHF_2-O	CH_3O	CH_3	CH_3O	H	2.7
21	CHF_2-O	CH_3O	CH_3O	CH_3O	H	28
22*	-O-CH_2-O-		CH_3	CH_3O	H	4.7
23	-O-CH_2-O-		CH_3O	CH_3O	H	33
24*	-O-CF_2-O-		CH_3	CH_3O	H	3.6
25	-O-CF_2-O-		CH_3O	CH_3O	H	80
26	-O-CF_2-O-		H	CH_3O	CH_3O	60
27*	-O-CH_2-CH_2-O-		H	CH_3O	H	3.4
28*	-O-CF_2-CHF-O-		H	CH_3O	H	6.1
29*	-O-CF_2-CHF-O-		CH_3	CH_3O	H	1.4
30	-O-CF_2-CHF-O-		CH_3O	CH_3O	H	32

t 1/2 (h) is the time in hours in which half of the compound decomposes at pH 5

Discussion

The object of the above comparative tests was to compare the chemical stability of compounds of FWC of SN 748,591 with the stability of structurally closely related compounds of the prior art. For this purpose compounds with various substituents in the benzimidazole part of the molecule have been selected which differ with regard to the substitution in the pyridine ring as follows: The prior art compounds (marked with an asterisk) are 4-alkoxy- (Compounds No. 1*, 7*, 11*, 27* and 28*), 4-alkoxy-3-alkyl- (No. 2*, 4*, 8*, 10*, 12*, 17*, 19*, 20*, 22*, 24* and 29*), 4-alkoxy-5-alkyl- (No. 13*) or 4-alkoxy-3,5-dialkyl--substituted (No. 3*) in the pyridine ring, whereas the compounds of FWC of SN 748,591, the essential structural feature of which is the dialkoxy-substitution in the pyridine ring, are 3,4-dialkoxy- (Compounds No. 5, 14, 18, 21, 23, 25 and 30), 4,5-dialkoxy- (No. 15 and 26) or 4,5-dialkoxy-3-alkyl-substituted (No. 6, 9 and 16).

For each compound of FWC of SN 748,591 listed in Table 2 (with the exception of Compound No. 26) there exists at least one prior art counterpart in Table 2 which is structurally closely related, i.e. which differs with regard to solely **one** substituent in the pyridine ring. In this connection, reference is made in particular to the following pairs of compounds:

Compounds No. 5 (R2 = CH_3O) and 4* (R2 = CH_3) ✓
Compounds No. 6 (R4 = CH_3O) and 4* (R4 = H) ✗
Compounds No. 9 (R4 = CH_3O) and 8* (R4 = H) ✗
Compounds No. 14 (R2 = CH_3O) and 11* (R2 = H) ✗
Compounds No. 14 (R2 = CH_3O) and 12* (R2 = CH_3) ✓
Compounds No. 15 (R4 = CH_3O) and 11* (R4 = H) ✗
Compounds No. 15 (R4 = CH_3O) and 13* (R4 = CH_3) ✓
Compounds No. 16 (R4 = CH_3O) and 12* (R4 = H) ✗
Compounds No. 18 (R2 = CH_3O) and 17* (R2 = CH_3) ✓
Compounds No. 21 (R2 = CH_3O) and 20* (R2 = CH_3) ✓
Compounds No. 23 (R2 = CH_3O) and 22* (R2 = CH_3) ?
Compounds No. 25 (R2 = CH_3O) and 24* (R2 = CH_3) ✓
Compounds No. 30 (R2 = CH_3O) and 28* (R2 = H) ✗
Compounds No. 30 (R2 = CH_3O) and 29* (R2 = CH_3) ✓

The general survey of all half-life values determined in the comparative tests as well as the comparison of the half-life values for the pairs of compounds

listed above clearly show that the chemical stability of the compounds of FWC of SN 748,591 is significantly greater than the stability of the compounds of the prior art. This greater stability in solution at pH 5 is obtained by the introduction of the second alkoxy substituent in the 3- or 5-position of the pyridine ring in addition to the 4-alkoxy substituent. From this improved stability and the related reduced reactivity at a pH of 5 it can be concluded that the dialkoxy substituted compounds will be more specific than those of the prior art. This combination of substituents fulfills the selection criterion described in the objective.

4. THAT, with regard to the comments set forth in the Advisory Action (Paper No. 14) of February 25, 1987, there is no reason to believe that any counterpart of any of the tested compounds reported herein would yield a significantly different result if R3 were ethoxy rather than methoxy. This view is supported by the fact that the substituent parameters (substituent constants), which are a measure for the relevant electronic substituent effects, are nearly identical for all members of the 1-3C-alkoxy group [5., 6.]. Furthermore, the results presented in the preceding table support a **general** conclusion that the stability of the dialkoxy- and dialkoxyalkylpyridine compounds is significantly superior to that of their alkoxy-, alkoxyalkyl- and alkoxydialkylpyridine counterparts with otherwise identical substitution pattern in the benzimidazole part of the molecule. This regularity, which means that of any pair of compounds - independent of the substituent(s) in the benzimidazole part - always the compound with the dialkoxysubstitution in the pyridine part of the molecule shows a significantly greater stability, was found without any exception. Therefore, it is justified to predict the superiority of the dialkoxy-substituted pyridines with regard to their stability characteristics also for compounds containing slightly modified substituents in the benzimidazole part, e.g. for compounds wherein R1 is CF_3CF_2-, CF_3CF_2CHF- or CHF_2CHF-, or wherein R1-O and R1' are simultaneously trifluoromethoxy or 1,1,2,2-tetrafluoroethoxy. The same is true for corresponding compounds wherein R1' is F or chloro-difluoromethoxy.

In re Johnson

5. THAT, the comparative test data in Table 2 prove that the compounds of FWC of SN 748,591 have stability characteristics which are unexpectedly superior to those of the compounds of the closest prior art.

THAT, it was not foreseeable that the compounds of FWC of SN 748,591, which have as an essential structural feature **two** alkoxy groups in the pyridine ring, would show a chemical stability which is so unambiguously superior over known compounds, having only **one** alkoxy group in the pyridine ring.

6. The undersigned Declarant declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed at Constance, Federal Republic of Germany,
this 24th day of April, 1987.

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(Dr. Uwe Krüger)

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